UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/179,002	10/26/1998	VIDYA BRAJ LOHRAY	DRF 3.0-019.	5185

45776 7590 02/23/2007

DR. REDDY'S LABORATORIES, INC.
200 SOMERSET CORPORATE BLVD
SEVENTH FLOOR,
BRIDGEWATER, NJ 08807-2862

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/179,002	LOHRAY ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,5,24, 30, 71 and 77* is/are allowed.

6)☒ Claim(s) *6-13,25-27,29-31,33,34,65-68,70-72,74,75,78-80,82,83 and 85-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,5-13,24-27,29-31,33,34,65-68,70-72,74,75,77-80,82,83 and 85-111.

DETAILED ACTION

Applicants' response, which included addition of new claims 87-111, cancellation of claims 28, 32, 69, 73, 76, 81, 84 and amendment to claims 1, 6-13, 24, 27, 29, 31, 33, 34, 65, 68, 70, 72, 74, 75, 80, 83, 85 and 86, file on 11/17/2006, is made of record.

Claims 1-3, 5-13, 24-27, 29-31, 33, 34, 65-68, 70-72, 74, 75, 77-80, 82, 83 and 85-111 are now pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-13, 27, 29, 31-34, 68, 70, 72, 74, 75, 80, 82, 83 and 85-111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected as it dependent on a rejected claim and shares the same indefiniteness.

1. Claims 10-13 are indefinite for more than one reason. Each of the claims 10-13, as recited, is product by process claim. They are dependent on claims 6-9 respectively. A product is a product irrespective of how it is made. The processes attributes are independent limitation and do not necessarily define the structural make-up of the product. A claim is not rendered patentably distinct by a process directed to its preparation even though the process may be patentable. Note "Determination of patentability in "product by process" claims is based on product itself, even though such claims are limited and defined by process, and thus product in such claim is

unpatentable if it is same as, or obvious from, product of prior art, even if prior product was made by different process" In re Thorpe 227 USPQ 964. Also note In re Brown, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972), the court held that "The lack of physical description in a product by process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established."

In the instant case, the compounds embraced in the claims 10-13 would be the same compound irrespective how these compounds are made. Specification has no showing that a process of making the compound would alter the structural make-up of the final product although the final product is same.

2. Claims 27, 29, 31-34, 68, 70, 72, 74, 75, 80, 83, and 85-111 are indefinite as they all lack an effective amount. As recited they read on any amount.

3. Claims 85-111 are indefinite as they all recite formula(I) of claim 77, but claim 77 does not recite formula (I). It is not clear what is intended.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25, 26, 66 and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making solvate. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt solvate or polymorph thereof. Specification is not adequately enabled as to how to make hydrate of compounds of formula (I) Specification has no example of solvate or polymorph of the instant compounds. Specification recites solvate or polymorph thereof but there is no enabling of such compounds.

The compound of formula I embrace quinazoline compounds substituted with variable groups, Ar, Y, X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7

Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of alkyl., aryl heteroaryl, heterocyclyl, substituted aryl, heteroaryl, arylalkyloxy, arylalkylthio etc would result in millions and millions of compounds. This is of course not the accurate number and the true number of compounds would far exceed this number of compounds. Thus, the genus embraced

in the claim is too large and there is no teaching of any solvate and polymorph of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates or hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the hydrate. In the instant case of hydrate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to hydrate

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of polymorphs, solvates and hydrates are unpredictable. See entire document especially page 18, right

column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

2. **The predictability or lack thereof in the art:**

Hence, the solvate and hydrate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of a solvate or hydrate of instant compound. Sixty four compounds were shown in the examples of the specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates. Hence it is clear that merely bring the compound with solvent or water does not result in solvate or hydrate and additional direction or guidance is needed to make them Specication has no such direction or guidance.

4. **The presence or absence of working examples:**

There is no working example of any solvate or hydrate formed. The claims are drawn to hydrate, yet the numerous examples presented all failed to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds

with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvate of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exist and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specication has no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate of the compound of formula I. As noted above, the genus embraces over million compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired hydrate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is

clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 6-9 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound of formula I wherein the phenyl ring of the quinazoline is unsubstituted or substituted with methoxy unsubstituted, Ar = unsubstituted phenylene, does not reasonably provide enablement for compound of formula I wherein the wherein the phenyl ring of the quinazoline is substituted with various reactive functional groups, Ar = substituted phenylene with various reactive functional groups, which are susceptible to variety of reagents used in the processes embraced in claims 6-9 and 65. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply:

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to a various processes of making compound of formula I. Specification is not adequately enabled as to how to make compounds of formula (I) wherein the said phenyl ring and phenylene ring are variously substituted with reactive

functional groups which are either susceptible to or incompatible with the reagents used in these processes. For simple example, consider claim 8 and 65 which recite hydrolysis to remove R^7 from compound of formula I. But as noted in claim 1, the compound of formula I bears variety of hydrolysable groups besides R^7 such as acyloxy groups, alkoxycarbonyl, aryloxycarbonyl, alkoxycarbonylamino, aryloxycarbonylamino etc., to name a few. These are also equally susceptible to the hydrolysis process of claim 8 and claim 65. Specification offers no guidance as to how to perform such an hydrolysis selectively to remove only desired R^7. In addition, the processes embraced include Wittig reactions, reduction, N-alkylation and C-alkylation etc., Again, reactive functional groups embraced as substituents on the phenyl ring and phenylene are equally susceptible or not compatible with these reagents. For example, if R^3 is formyl or acyl group, they can also react with the Wittig reagent shown in claim 6, process a). How to get a selective reaction with the side chain aldehyde group is not taught therein. Whether the Wittig reaction would work in the instant case with amino group carboxylic acid group, sulfonic acid , hydroxyl group is group not addressed. Normally such groups are incompatible with Wittig reagents. Similarly, in claim 6, process c) recites an alkylation. But it is not clear how the side chain will be appended on a carbon. That is how would one get a C-alkylation product by reacting IIIc with IIId. It is also not clear how would one get selective N-alkylation or C-alkylation of the pyrimidine ring when equally reactive groups such as amino hydroxy etc., are present in phenyl ring and phenylene ring. Esters, nitro groups cyano, halogen etc can also undergo reduction. The same applies to remaining processes as well as the process of claims 7-9.

Specification has no teaching or suggestion as to how to make the said compounds using the processes of claim 6-9

Specification offers no teachings or suggestion as to how to perform the these processes in presence of these reactive groups. Thus, presence of such reactive groups are chemically incompatible the processes embraced in the instant claims.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

4. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the process of making compound of formula I, when reactive substituents or chemically incompatible substituents are present in the starting material.

5. The presence or absence of working examples:

Although examples 1-62 show the sòme of the process, they are limited to quinazoline with no substituents or methoxy group and unsubstituted phenylene with no reactive functionality. There are no representative examples showing the viability of the process for plurality of reactive substituents embraced in the instant claims.

6. The breadth of the claims:

Specification has no support, as noted above, for processes generically embraced in the claim language would lead to desired compound of formula I with said

reactive groups and there is also no valid chemical reasoning for one trained in the art to expect that all these functional groups would be inert toward Wittig reagent, the reducing agent and hydrolyzing agents embraced in the process claims.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula I embraced in the instant claims .

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion

is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claims 27, 29, 31, 33, 68, 69, 72, 74, 80, 83, 85 and 87-111 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating diabetes, does not reasonably provide enablement for treating or preventing any or all diseases or any or all cancers generically embraced in these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant method of use claims 27, 29, 31, 33, 68, 69, 72, 74, 80, 83, 85 and 87-111 are drawn to preventing and treating large list of diseases including any or all caner based on the mode of action of instant compounds as HMG CoA reductase inhibitors, PPARa, PPARg agonists etc. in general.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of HMG CoA reductase and or as PPARa and PPARg agonism by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibition of HMG CoA reductase and or as agonist of PPARa and PPARg, based on

limited assay, it is claimed that preventing and treating any or all diseases including any or all cancers in general, which there is no enabling disclosure.

The scope of the claims includes preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism, type 11 diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), improving cognitive functions in dementia, diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer for which there is no enabling disclosure. In addition, the scope of these claims includes preventing and treating various cancers, which would include including lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland,

sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have HMG CoA reductase inhibitory activity and have agonist of PPARa and PPARg and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as HMG CoA reductase inhibitor and or agonist of PPAR that would be useful for all sorts of diseases and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The scope of the claims involves millions of compounds of claim 1 as well as the thousand of diseases embraced by the term cancer and other diseases.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper

proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat proliferative diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The term " prophylaxis" actually means to prevent spread of a disease (as per Meriam Webster's Dictionary). "To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. Further, there is no evidence on record which demonstrates that the in-vitro screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art at the time of instant invention is indicative of the requirement for undue experimentation. See Khan et al., Diabetes Care 25(4), 708-771, 2002 and Iida et al., FEBS Letters 520, 177-181, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn to besides treatment, prevention of any and all cancer and variety of diseases and disorders. However, specification provides no support for preventing all or any disorders. In fact based on the specification and examples, it appears that the instant compounds are

mainly PPAR and HMG CoA reductase inhibitors and may be useful for treating disorders of diabetes wherein these receptor are implicated. Specification has not provided any evidence or nexus that because of the mode of action of the instant compound, the compound would be useful for preventing and treating all or any said disorders and cancers. Such a reasonable correlation is necessary to demonstrate such utilities. See Ex parte Stevens, 16 USPQ 2d 1379 (BPAI 1990); Ex parte Busse et al., 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). The evidence presented in this case does not show such utilities related to 'prevention', but only warrants further study.

2) The state of the prior art: Recent publications expressed that the inhibition effects of HMG CoA reductase and agonists of PPAR are unpredictable and are still exploratory and agonists See Khan et al., and Iida et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating and preventing all the said diseases and any or all cancers by the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating and or preventing any or all cancers or various diseases positively recited in the instant claims

and the state of the art is that the effects of HMG CoA reductase inhibitors and agonists of PPAR are unpredictable.

6) The breadth of the claims: The instant claims embrace treating and preventing any or all cancers and various diseases with huge genus of compounds.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action but now includes newly added claims and excludes some cancelled claims. Applicants' traversal is not persuasive.

First of all, as noted above, instant claims are reach through claims. Again, based on the mode of action, based on the limited assays (pages 90-96), applicants are asserting that any disease wherein PPAR is present can treated and can be prevented for which there is no evidence provided. Applicants rely on two articles but both of which clearly suggest further experimentation. In fact one the article is a protocol for clinical studies.

Secondly, applicants assert that diabetes can be prevented and any disease related Syndrome X can be prevented but have not offered any evidence showing such is the case. Currently there are several antidiabetic agents which show similar glucose lowering activity but they have not prevented diabetes.

Thirdly, applicants assert the said compounds can be used to prevent diabetes another diseases stated therein. Yet claims 31, 33, 34 and other incorporate additional active ingredients. If the instant compounds are able to prevent the said diseases why would one need additional active ingredients ?. Note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

Hence, this rejection is proper and is maintained.

Allowable Subject Matter

Claims 1-3, 5, 24, 30, 71 and 77 are allowed.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

2/19/2007